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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/527,222	12/21/2005	Hansjorg Eibl	HUBR-1279	3227

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EXAMINER	
KISHORE, GOLLAMUDI S	
ART UNIT	PAPER NUMBER
1612	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/527,222	EIBL ET AL.	
	Examiner	Art Unit	
	Gollamudi S. Kishore, Ph.D	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *9-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3-10-05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims included in the prosecution are 9-18.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 9-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear as to what applicant intends to convey by “A thermo labile liposome having a controlled release temperature for the liposome content" in claim 9. Does applicant mean "for the release of the contents"? or the liposome contents have the controlled release temperature? Are these empty liposomes? (the dependent claim recites active compound). If so, nothing will be released.

It is unclear as to whether the limitations in parenthesis are indeed the limitations as recited in claim 12. The examiner suggests “dipalmitoylphosphatidylcholine’ and 'distearoylphosphatidylcholine’ instead of dipalmitoyllecithin and distearoyllecithin, if DPPC and DSPC are the ones which are used. Naturally occurring lecithin has different fatty acids where as the fatty acid chains in DPPC and DSPC are specific.

According to claim 9, the liposome has both phosphatidylcholine and phosphatidyl-oligoglycerol. What is being conveyed by the dependent claim 18 which recites “liposome consists essentially of said at least one phosphatidylcholine? These liposomes have only phosphatidylcholine?

3. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c). Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, claim 14 recites the broad recitation ether lysolecithin, and the claim also recites hexadecyl phosphocholine which is the narrower statement of the range/limitation.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 9-11, 13, 15-18 are rejected under 35 U.S.C. 102(b) as being anticipated by DE 196 22 224 of record.

DE discloses liposomes containing liposomes containing dipalmitoylphosphatidylcholine (DPPC) and dipalmitoyl phosphatidyloligoglycerols in an amount of approximately 5 to 15 %. Cholesterol is optional (0014, 0018, 0022, Examples of English translation).

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 9-13 and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over DE 196 22 224 or Maruyama et al (international Journal of Pharmacology, 1994) of record.

DE discloses liposomes containing liposomes containing dipalmitoylphosphatidylcholine (DPPC) and dipalmitoyl phosphatidyloligoglycerols in an amount of approximately 5 to 15 %. Cholesterol is optional (0014, 0018, 0022, Examples of English translation).

Maruyama discloses liposomes containing phosphatidylcholine (DSPC), phosphatidyloligoglycerol (DPP-PG) and a labeling substance (Table 1 on page 104).

What is lacking in DE and Maruyama is the teaching of instant amounts of phosphatidyloligoglycerol. However, in the absence of showing the criticality, it is deemed obvious to one of ordinary skill in the art to vary the amounts of this compound to obtain the best possible results.

7. Claims 9-13 and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 99/52505 in view of DE 196 22 224 or Maruyama (International Journal of Pharmaceutics, 1994).

WO discloses liposomes containing imaging agent. The liposomes are made of phosphatidylcholine (DSPC and DPPC) and dipalmitoyl phosphatidylglycerol (DPPG). DSPC: DPPC: DPPG are taught in a ratio of 28.5/66.5/5 (example 2 and 20). WO does not teach the use of phosphatidyloligoglycerol.

DE discloses phosphatidyloligoglycerols and liposomes made of these oligoglycerols. DE further teaches the oligoglycerols increase the circulation time of the liposomes (0025 of English Translation). DE teaches about 12% dipalmitoyl phosphatidyloligoglycerols in example 2.

Maruyama discloses liposomes containing phosphatidylcholine (DSPC), phosphatidyloligoglycerol (DPP-PG) in the instant amount, and a labeling substance (Table 1 on page 104). Maruyama further teaches that the oligoglycerols prolong the liposome circulation in vivo (abstract).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of WO and DE or Maruyama and substitute the prior art's dipalmitoyl phosphatidylglycerol with the instant dipalmitoyl

phosphatidyloligoglycerols. One would have been motivated to do so with a reasonable expectation of success since DE and Maruyama teach that the presence of this compound in liposomes increases the circulation time of the liposomes.

8. Claims 9-13 and 15-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 05 194 92 in view of DE 196 22 224 or Maruyama cited above by themselves or in combination.

JP teaches that liposomes made of dipalmitoyl phosphatidylcholine and a negatively charged 1, 2 diacyl glycerophosphatides in weight ratios of 20: 1 to 8:2. According to JP the DPPC and the negatively charged lipid in a specific proportion provides controlled release and temperature sensitivity (English Abstract and claims 1-2).

JP however, does not teach that the negatively charged lipid to be phosphatidyloligoglycerol.

Maruyama discloses liposomes containing phosphatidylcholine (DSPC), phosphatidyloligoglycerol (DPP-PG) in the instant amount, and a labeling substance (Table 1 on page 104). Maruyama further teaches that the oligoglycerols prolong the liposome circulation in vivo (abstract).

DE discloses liposomes containing liposomes containing dipalmitoylphosphatidylcholine (DPPC) and dipalmitoyl phosphatidyloligoglycerols in an amount of approximately 12 % (example 2). Cholesterol is optional (0022 of English translation).

It would have been obvious to use the negatively charged oligoglycerols of DE in the thermo sensitive liposomes containing negatively charged phosphatidylglycerol of JP with the expectation of obtaining similar results since DE teaches that these compounds can be used to make liposomes in combination with saturated lipids such as DPPC and Maruyama teaches that the circulation times of the liposomes are increased with the incorporation of the oligoglycerols. Although JP, Maruyama and DE do not teach the use of both saturated lipids, DPPC and DSPC, since these are known to be used in the formation of liposomes as evident from the references, it would have been obvious to one of ordinary skill in the art to use them together and vary their amounts with a reasonable expectation of success.

9. Claims 13-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over JP 05 194 92 in view of DE 196 22 224 or Maruyama cited above by themselves or in combination as set forth above, further in view of Aneja (6,284,267).

The teachings of JP, DE and Maruyama have been discussed above. What is lacking in these references is the inclusion of an alkyl phosphocholine such as hexadecyl phosphocholine.

Aneja while disclosing liposome formulations containing active agents teaches that hexadecyl phosphocholine is an anti-neoplastic agent (Table 2 and Table 3 A on col. 27).

It would have been obvious to one of ordinary skill in the art to use hexadecyl phosphocholine in JP, DE and Maruyama if the intended purpose is to deliver an anti-

neoplastic agent with a reasonable expectation of success since Aneja teaches that this compound is an anti-neoplastic agent and could be used in liposomes.

Double Patenting

10. Claims 9-13 and 15-18 are provisionally rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-4 and 6 of copending Application No. 10/468,116. Although the conflicting claims are not identical, they are not patentably distinct from each other because both are drawn to same thermo labile liposomes containing the same components. Instant claims differ from the claims in the copending application in that the amounts of the phosphatidyloligoglycerol in the copending application are in the range of 2-15 % whereas instant amounts are 15 to 70 % In addition, instant claims recite the limitation “comprising. Since phospholipids are known to form bilayer liposomes with or without the addition of any other component it would have been obvious to one of ordinary skill in the art to add additional components or vary their amounts with a reasonable expectation of forming liposomes.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 9-13 and 15-18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11-48 of US 6,413,543.

Although the conflicting claims are not identical, they are not patentably distinct from each other because both are drawn to same thermo labile liposomes containing the same components. Instant claims differ from the claims in the US '543 in that the amounts of the phosphatidyloligoglycerol is in the range of 1-50 % whereas instant amounts are 15 to 70 %; it would have been obvious to one of ordinary skill in the art to vary their amounts with a reasonable expectation of forming liposomes. The instant claims also are rejected over the method of making the liposomes, since a restriction has not been made. Thus, one would necessarily have possession of the product, i.e. liposome by following the method of making the liposomes.

12. Claims 13-14 are provisionally rejected on the ground of nonstatutory obviousness- type double patenting as being unpatentable over claims 1-4 and 6 of copending Application No. 10/468,116 in view of Aneja (6,284,267). Although the conflicting claims are not identical, they are not patentably distinct from each other because both are drawn to same thermo labile liposomes containing the same components. Instant claims differ from the claims in the copending application in that the amounts of the phosphatidyloligoglycerol in the copending application are in the range of 2-15 % whereas instant amounts are 15 to 70 % In addition, instant claims recite the limitation “comprising. Since phospholipids are known to form bilayer liposomes with or without the addition of any other component it would have been obvious to one of ordinary skill in the art to add additional components or vary their amounts with a reasonable expectation of forming liposomes. Although instant claims do not recite alkyl phosphocholines such as hexadecyl phosphocholine, it would have

been obvious to one of ordinary skill in the art to use hexadecyl phosphocholine if the intended purpose is to deliver an anti-neoplastic agent with a reasonable expectation of success since Aneja teaches that this compound is an anti-neoplastic agent and could be used in liposomes.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. 13. Claims 13-14 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11-48 of US 6,413,543. Although the conflicting claims are not identical, they are not patentably distinct from each other because both are drawn to same thermo labile liposomes containing the same components. Instant claims differ from the claims in the US '543 in that the amounts of the phosphatidyloligoglycerol is in the range of 1-50 % whereas instant amounts are 15 to 70 %; it would have been obvious to one of ordinary skill in the art to vary their amounts with a reasonable expectation of forming liposomes. The instant claims also are rejected over the method of making the liposomes, since a restriction has not been made. Thus, one would necessarily have possession of the product, i.e. liposome by following the method of making the liposomes. Although instant claims do not recite alkyl phosphocholines such as hexadecyl phosphocholine, it would have been obvious to one of ordinary skill in the art to use hexadecyl phosphocholine if the intended purpose is to deliver an anti-neoplastic agent with a reasonable expectation of success

since Aneja teaches that this compound is an anti-neoplastic agent and could be used in liposomes.

References AE and AF are not considered since no copies have been provided.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/
Primary Examiner, Art Unit 1612

GSK